[12780/101]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Leonard et al.	
For:	VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE	Examiner: Ford
		Art Unit: 1645
Filed:	November 8, 2000	
Serial No.:	09/708,352	
Customer No.:	26646	

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APPEAL BRIEF TRANSMITTAL

SIR:

Transmitted herewith for filing in the above-identified patent application, please find an Appeal Brief pursuant to 37 C.F.R. § 41.37.

Please charge the small entity Appeal Brief fee of **$250.00**, and any other fees that may be required in connection with this communication to the deposit account of **Kenyon & Kenyon LLP**, deposit account number **11-0600**.

Applicants hereby request a **five-month extension of time** for submitting the Appeal Brief. The extended period for submitting the Appeal Brief expires on May 27, 2006. Please charge the **$1,080.00** small entity extension fee and any other fee that may be required to Deposit Account No. 11-0600. A duplicate of this Transmittal is enclosed.

Respectfully submitted,

Dated: MAY 22, 2006

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APPEAL BRIEF

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Real Party in Interest

The real party in interest for U.S. Patent Application Serial No. 09/708,352 is:

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96, rue de la Victoire, 75009 Paris
FRANCE

Related Appeals and Interferences

There are no related appeals or interferences.

Status of Claims

Claims 1, 3-12, and 29-56 are pending. Claims 1, 3-12, and 29-56 are under rejection and are being appealed. Claims 2, and 13-28 have been canceled.

Status of Amendments

An Amendment under 37 C.F.R. §1.116 (an Amendment after Final) was filed October 24, 2005, 2005 but was not entered.

Summary of Claimed Subject Matter

The invention defined by independent **claim 1** is a vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species {**specification, page 4, lines 7-8**} comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype {**specification, page 4, lines 8-9**}, an adjuvant {**specification, page 8, lines 7-8**}, and a pharmaceutically acceptable excipient {**specification, page 4, lines 9-10**}, and wherein the adjuvant does not include saponin {**specification, page 8, lines 7-26, particularly line 21**} and the clinical disease includes respiratory pneumonia {**specification, at Example 7, page 21, line 27 to page 22, line 22, and the abstract**}.

The invention defined by independent **claim 5** is a vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species {**specification, page 4, lines 7-8**} comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype {**specification, page 4, lines 8-9**}, an adjuvant {**specification, page 8, lines 7-8**}, and a pharmaceutically acceptable excipient {**specification, page 4, lines 9-10**}, wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A {**specification, page 6, line 20**}, biotype B {**specification, page 6, line 20**} and biotype C {**specification, page 6, line 20**}, and wherein the adjuvant does not include saponin {**specification, page 8, lines 7-26, particularly line 21**}.

The invention defined by independent **claim 8** is a vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species {**specification, page 4, lines**

7-8} comprising at least two inactivated or attenuated *Mycoplasma bovis* biotypes **{specification, page 9, lines 1-2}** and a pharmaceutically acceptable excipient **{specification, page 4, lines 9-10}**.

The invention defined by independent **claim 29** is a vaccine which is protective against *Mycoplasma bovis* mastitis in a bovine species **{specification, at Example 5, pages 18-20, particularly page 19, lines 17-32, abstract}** comprising at least one inactivated or attenuated Mycoplasma *bovis* biotype **{specification, page page 4, lines 8-9}** and a pharmaceutically acceptable excipient **{specification, page 4, lines 9-10}**.

The invention defined by independent **claim 52** is a whole-cell vaccine **{specification, page 16, lines 22-28}** which is protective against *Mycoplasma bovis* clinical disease in a bovine species **{specification, page 4, lines 7-8}** comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype **{specification, page 4, lines 8-9}** and an adjuvant selected from the group consisting of: an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; and paraffin oil **{specification, page 8, lines 16-26 and page 11, lines 3-4}**.

The invention defined by independent **claim 56** is a vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species **{specification, page 4, lines 7-8}** comprising at least one attenuated *Mycoplasma bovis* biotype **{specification, page 4, lines 8-9}** and a pharmaceutically acceptable excipient **{specification, page 4, lines 9-10}**, wherein the clinical disease includes respiratory pneumonia **{specification, at Example 7, page 21, line 27 to page 22, line 22, and the abstract}**.

Grounds of Rejection to be Reviewed on Appeal

The following grounds of rejection are present in this appeal:

(1) claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 have been rejected as anticipated under 35 U.S.C. §102(b) by Boothby, Immunologic Responses to Mycoplasma bovis, University Microfilm International (Dissertation) 1-172, 1982 (Boothby I);

(2) claims 1, 4, 5, 7, 29, 30, and 56 have been rejected as anticipated under 35 U.S.C. §102(b) by Thorns et al., 1980, Res. Vet. Sci. 29:328-332 (Thorns); and

(3) claims 1, 3-12, and 29-56 have been rejected as obvious under 35 U.S.C. §103(a) over Boothby I in view of Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat) and Thorns.

Argument

Ground of rejection 1

Are claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 anticipated under 35 U.S.C. §102(b) by Boothby, Immunologic Responses to Mycoplasma bovis, University Microfilm International (Dissertation) 1-172, 1982 (Boothby I)?

Claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 are rejected as being anticipated by Boothby I. These claims do not stand or fall together, but instead should be grouped according to the subheadings below.

Claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 (all the claims subject to this rejection)

Boothby's vaccine does not anticipate claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 because there is a clear difference between the Appellants' vaccine and Boothby I's vaccine. Boothby I's vaccine produces a very unfavorable reaction - all of Boothby I's animals showed hypersensitivity (see Boothby I, page 136, 3rd paragraph: "All groups receiving adjuvant preparations developed delayed-type hypersensitivity ...").

In contrast, the presently claimed vaccines do not cause unfavorable reactions. See the specification at page 23, lines 2-3: "No unfavorable reactions resulting from the vaccine's use have been reported;" page 23, lines 14-15: "No unfavorable reactions in animals receiving the product have been reported;" page 20, line 1: "No injection reactions were observed;" and the abstract: "These vaccines demonstrate no undesirable side effects ..."

This is a real difference between the Appellants' vaccine and Boothby I that must be due to the nature of the vaccine, and thus indicates that the vaccine of Boothby I does not anticipate the presently claimed vaccine.

Claims 5, 6, and 54

Claim 5 and dependent claims 6 and 54 require that the vaccine comprises particular biotypes that are not disclosed in Boothby I. Claims 5, 6, and 54 each require at least one biotype selected from the group consisting of biotype A, biotype B and biotype C. Boothby I does not disclose biotype A, B, or C. Thus, Boothby I cannot anticipate these claims.

Claims 29, 30, and 40-44

Claims 29, 30, and 40-44 all contain the limitation that the claimed vaccine must be "protective against *Mycoplasma bovis* mastitis in a bovine species." The Examiner argued that this limitation is merely an "intended use" and therefore is not sufficient to avoid anticipation by Boothby I. See the Office Action, dated May 25, 2005, page 4, line 17 to page 5, line 12.

The Appellants do not agree. Being protective against mastitis is not simply an intended use but rather is a functional characteristic of the vaccine itself. The characteristic of being protective against mastitis distinguishes the claims over the prior art, such as the vaccine disclosed in Boothby I. The evidence of record demonstrates that prior art vaccines, such as Boothby I's, were not protective against mastitis. Persons skilled in the art, having knowledge of Boothby I and other prior art, did not view the then-existing vaccines as being protective against mastitis.

For example, Heller et al., 1993, Vet. Microbiol. 37:127-133 (Heller), when referring to methods of controlling the spread of *Mycoplasma bovis*-caused mastitis, did not mention that one should vaccinate to control mastitis but instead stated that culling is necessary. See page 127: "To control the spread of this disease, an early detection of

the pathogen is crucial since the removal and culling of infected cows is necessary to prevent fresh infections."

Hanson, (September, 2001) Bovine Veterinarian 4-8 (Hanson I) and Hanson, (October, 2001) Bovine Veterinarian 12-20 (Hanson II), described methods to prevent mastitis or mitigate its effects, but the methods do not include vaccination, indicating that no vaccine protective against mastitis was known to the art. This failure to mention vaccination is telling, since there clearly was recognition in the art that *Mycoplasma bovis*-caused mastitis was a serious problem. For example, Hanson I, at page 4, quotes a veterinarian as follows:

> "*Mycoplasma* mastitis is a doubly insulting disease," says Blackmer. "Not only can it be remarkably contagious when it is present but it absolutely does not respond to antibiotic therapy. In fact, treatment can actually cause epidemics, because it frequently is spread by unsound intramammary therapy practices."

If vaccination had been available to combat a problem as serious as *M. bovis*-caused mastitis, Heller, Hanson I, and Hanson II would have been expected to mention it, but they did not.

The Office Action dated May 25, 2005, page 5, lines 5-7, refused to consider this evidence, stating: "Applicant's referral to other publications (Heller et al, 1993, Hanson, September 2001 and Hanson, October 2001) to support their position is irrelevant since Boothby teach the claimed vaccine compositions." [emphasis added] However, this misunderstands the import of the evidence. Heller and the two Hanson publications demonstrate that Boothby I does not teach the claimed vaccines. The Appellants submit that the Office Action has assumed the issue to be decided - whether Boothby I discloses the claimed vaccines - before considering all the evidence that should be used to decide that issue. The U.S. Patent & Trademark Office has the burden of proving a case of anticipation, based upon reasoned arguments, after considering all relevant evidence. The Appellants submit that this has not been done.

The Office Action did not explain why, if Boothby I provided a vaccine against mastitis, the art was still recommending culling and other non-vaccine approaches as the only methods of combating mastitis nearly twenty years after Boothby I's disclosure became public.[1] Based on the record as it currently stands, the inevitable conclusion is that Boothby I's vaccine was not protective against mastitis, and thus could not have been the same as the claimed vaccine.

The Office Action dated May 25, 2005 cited *In re Casey*, 370 F. 2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F. 2d 937, 136 USPQ 458 (CCPA 1963) in support of its position with respect to the limitation of protection against mastitis.

Casey is not applicable to the present fact pattern because the functional properties of the claimed device in *Casey* were found to be inherently disclosed in the Kienzle prior art reference. See 370 F. 2d at 941, 152 U.S.P.Q. at 238, where the Court of Customs and Patent Appeals agreed with the reasoning of the Board of Appeals and stated: "The rationale of the board clearly deducible from the language employed is that the Kienzle apparatus as it obviously must be constructed would inherently perform all of the functions called for in claim 1 ..." In the present application, the functional property of being protective against mastitis is not found in the prior art, either explicitly or inherently.

In *Otto*, the claims were rejected for obviousness over a large number of references that collectively disclosed all the limitations recited in the claims. That is not the case here, where the record contains no prior art, either alone or in combination, disclosing the limitation of "protective against bovine mastitis." Instead, the record contains compelling evidence that the prior art lacked this limitation.

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[1] Boothby I is dated 1982. Heller is dated 1993. Hanson I and Hanson II are dated 2001.

A much more recent decision, in the Federal Circuit, which specifically dealt with functional characteristics of product claims, and which is therefore particularly applicable to the present application is *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F. 3d 989, 54 U.S.P.Q. 2d 1227 (Fed. Cir. 2000). In *Union Oil*, the claims at issue were directed to gasolines that were defined as being suitable for combustion in automotive engines. See 208 F. 3d at 995, 54 U.S.P.Q. 2d at 1231:

> The claims of the '393 patent recite either "[a]n unleaded gasoline suitable for combustion in an automotive engine" or "[a]n unleaded gasoline fuel suitable for combustion in a spark ignition automotive engine."

The district court construed these claims to cover only automotive fuels, not also aviation or racing fuels. This was primarily due to the specification's teaching that the functional characteristic of being suitable for use in automotive engines addressed the problem the invention was directed toward, together with the claims' recitation of that characteristic. This resulted in a finding that the quoted functional language was a real limitation of the claims, and not just an intended use. See 208 F. 3d at 995-996, 54 U.S.P.Q. 2d at 1231-1232:

> The district court's interpretation also finds extensive support in the specification. The patentees described the problem that their invention addressed:
>
> > One of the major environmental problems confronting the United States and other countries is atmospheric pollution (i.e., "smog") caused by the emission of gaseous pollutants in the exhaust gases from automobiles. This problem is especially acute in major metropolitan areas, such as Los Angeles, Calif., where the atmospheric conditions and the great number of automobiles account for aggravated air pollution.
>
> ...
>
> The patentees tailored their research and their patent to ordinary fuels for use in standard passenger cars. Thus, the claim language, further informed by the specification, shows that the district court correctly read the claims to cover ordinary automotive fuel.

> Because the '393 patent covers only standard automotive fuel, the district court correctly determined that specialty fuels within other limitations of the claims do not anticipate under 35 U.S.C. § 102.

As in *Union Oil*, claims 29, 30, and 40-44 of the present application recite the functional characteristic at issue - "protective against *Mycoplasma bovis* mastitis." Also as in *Union Oil*, the present specification stresses the problem of mastitis and teaches that the vaccines of the present invention address that problem by providing actual data showing the vaccines to be protective against mastitis. See the specification, page 2, lines 1-11:

> Diseases caused by mycoplasmas are often resistant to antimicrobial therapy, leaving no effective means of treatment. Consequently, the only effective control method is to cull animals from a herd. This has enormous economic implications in the dairy industry where losses are measured by the value of the culled animals as well as the impact on both milk quality and quantity due to clinical and subclinical infections. Mycoplasma infections resulting in bovine mastitis are increasing in prevalence and geographical distribution. In the United States, this higher prevalence is due to a larger and-more intense cattle production industry in which herds are rapidly expanding, placing them at greater risk. Increased incidence of *M. bovis* infection and related infectious disease in dairy herds has been noted worldwide (Jasper, DE 1982, J. Amer. Vet. Med. Assn. 181:158-162).

See also Example 5, pages 18-20, where a large decrease in the number of mastitis cases occurred in a herd that was vaccinated with the vaccine of the present invention. See in particular page 19, lines 17-32:

> Comparative results were used to measure efficacy of the vaccine. Samples taken from all animals presenting with clinical mastitis were cultured by an independent laboratory to monitor the absence or presence of Mycoplasma bovis infection of the mammary gland. Field evaluations were made by comparing clinical incidence of mastitis caused by Mycoplasma bovis following herd vaccination to the base line herd incidence prior to vaccination. Results were as follows:
>
> Pre Vaccination Base Line Incidence:
> 155 confirmed positive clinical Mycoplasma bovis infections
>
> Post Vaccination Herd Incidence:
> 1st year following vaccination:
> 24 confirmed positive clinical Mycoplasma bovis infections
> 2nd year following vaccination:
> 1 confirmed positive clinical Mycoplasma bovis infection.

In view of the Federal Circuit's guidance in *Union Oil* as to how such a claim recitation should be construed, the recitation of "protective against *Mycoplasma bovis* mastitis" is a true limitation of claim 29, 30, and 40-44 and serves to distinguish these claims over the prior art.

Even if the recitation of "protective against bovine mastitis" is viewed as an intended use, this rejection should be withdrawn. In connection with the interpretation of this recitation as an intended use, the Office Action cited *Casey* and *Otto* as support for the proposition that (sentence bridging pages 4 and 5): "If the prior art is capable of performing the intended use, then it meets the claim." This proposition is inapplicable here, because the evidence of record shows that the prior art is not capable of protecting against mastitis.

Where the prior art product was not capable of performing the intended use, the Board of Patent Appeals and Interference held that claims reciting the intended use were not anticipated. In *Ex parte Hervy A. Morris* (available at 1998 WL 1736155), a claim directed to a cutting device recited "to deflect the liquid jet stream when the cutting element is moved to the idle position." The Examiner interpreted this recitation as an intended use and rejected the claim over *Casey* and *Otto*, stating: "If the prior art structure is capable of performing the intended use, then it meets the claim."

> [t]he phrase "to deflect the liquid-jet stream ....." should not be construed as defining structure. It does not describe any structure; it merely expresses what the disk is desired to do. However, it has well been established that, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In re Casey, [370 F.2d 576, 580,] 152 USPQ 235[[, 238] (CCPA 1967); In re Otto, [312 F.2d 937, 940,] 136 USPQ 458, 459 (CCPA 1963).

Ex parte Hervy A. Morris, page 2.

The Board of Patent Appeals and Interference reversed this rejection, stating:

> Although we appreciate the examiner's position, we do not agree with his argument, because in our view the disk 620 of Driver [the prior art relied on by the Examiner] is not capable of performing the intended use recited, i.e., of "deflect[ing] the liquid-jet stream when the cutting element is moved to the idle position."

Ex parte Hervy A. Morris, page 2.

The evidence of record shows that Boothby I's vaccines were not "capable of performing the intended use" because the evidence of record shows that Boothby I's vaccines were not protective against mastitis. Accordingly, *Casey* and *Otto* are not applicable and claims 29, 30, and 40-44 are not anticipated by Boothby I.

Claims 52 and 55

Claims 52 and 55 recite that the vaccine comprises an adjuvant selected from a group that does not include the adjuvants listed in Boothby I.[2] Therefore, Boothby I does not anticipate claims 52 and 55.

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[2] At page 131, Boothby I discloses the use of the following adjuvants:
Freund's incomplete adjuvant
N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP)
Amphotericin B
Combined magnesium/aluminum hydroxide
Killed *Bordatella pertussis*

Ground of rejection 2

Are claims 1, 4, 5, 7, 29, 30, and 56 anticipated under 35 U.S.C. §102(b) by Thorns et al., 1980, Res. Vet. Sci. 29:328-332 (Thorns)?

Claims 1, 4, 5, 7, 29, 30, and 56 are rejected as being anticipated by Thorns. These claims do not stand or fall together, but instead should be grouped according to the subheadings below.

Claims 1, 4, 5, 7, 29, 30, and 56 (all of the claims subject to this rejection)

There is a clear difference between the presently claimed vaccines and Thorn's mycoplasma strains. The presently claimed vaccines do not cause unfavorable reactions. See the specification at page 23, lines 2-3: "No unfavorable reactions resulting from the vaccine's use have been reported;" page 23, lines 14-15: "No unfavorable reactions in animals receiving the product have been reported;" page 20, line 1: "No injection reactions were observed;" and the abstract: "These vaccines demonstrate no undesirable side effects ..."

All of the strains in Thorns caused some kind of histopathological change. See the right column in Table 1 on page 329, which shows that only the control (i.e., no *Mycoplasma bovis*) injections resulted in no histopathological changes.

Claims 1, 4, 5, 7, 29, 30, and 56 all recite "vaccines" that are "protective" against diseases caused by *Mycoplasma bovis* in bovines. Thorns does not even disclose a vaccine. Thorns discloses only attenuated strains of *Mycoplasma bovis* that were injected into mice. There is no disclosure in Thorns that the attenuated strains were protective against any disease in the injected mice, and certainly not against any disease

in bovines. Thorns does not even disclose any data that indicate the attenuated strains caused any stimulation of the immune systems of the mice against *Mycoplasma bovis*.

Thorns showed that highly passaged strains were attenuated in the sense that the highly passaged strains themselves did not cause responses such as inflammation or abnormal glands to the same degree as low passaged strains. Thus, Thorns disclosed attenuated *Mycoplasma bovis* strains. But claims 1, 4, 5, 7, 29, 30, and 56 are not directed simply to attenuated strains. They are directed to attenuated strains that are capable of functioning as vaccines. Thorns contains no evidence that the attenuated strains disclosed therein could function as vaccines, to protect against disease caused by later exposure to *Mycoplasma bovis*. In particular, Thorns provided no evidence that the mice that were given the attenuated strains were protected from disease when later challenged with *Mycoplasma bovis*. Apparently, Thorns did not even challenge the mice.

The Office Action concluded that, since Thorns's highly attenuated strains did not cause disease themselves, they must have been able to protect against disease, i.e., that the attenuated strains were vaccines. See the Office Action dated May 25, 2005, page 6, lines 2-6:

> Thorns et al teach that all mice that were inoculated with *M. bovis* passaged over 91 times had normal glands and showed not signs of systematic response (page 329, Table 1). Therefore, the mice vaccinated with *M. bovis* passaged over 91 times appeared to be protected against systematic response.

But this logic is fundamentally flawed. It confuses one characteristic - the lack of ability to cause disease - with another, not necessarily related, characteristic - the ability to protect against disease. The Office Action provided no evidence that an attenuated

strain having the former characteristic would necessarily have the second characteristic as well.

Moreover, the authors of Thorns stated that their strains were not vaccines. The authors considered that the work they disclosed only provided information and a starting point for research that might someday "perhaps" lead to the production of a vaccine against *Mycoplasma bovis*. In view of this statement, the strains described in Thorns could not already be vaccines. See page 332, right column, 3rd paragraph:

> Whatever mechanisms the virulent strains have lost or modified, they should provide further insight into the pathogenesis of *M. bovis* mastitis which could perhaps lead to a stable vaccine for this disease. [emphasis added]

Claims 1, 4, 5, and 7

Claims 1, 4, 5, and 7 recite "an adjuvant." Thorns does not disclose an adjuvant. For this reason, Thorns does not anticipate claims 1, 4, 5, and 7.

Claims 29, 30, and 56

Claims 29, 30, and 56 recite the limitations that the claimed vaccines must be "protective against *Mycoplasma bovis* mastitis" (claims 29 and 30) or "protective against *Mycoplasma bovis* clinical disease ... wherein the clinical disease includes respiratory pneumonia" (claim 56). As discussed above in connection with the rejection over Boothby I, these recitations are not simply an "intended use" but instead are functional limitations that confer patentable distinction on the claims. Thorns contains no showing that the attenuated strains disclosed therein are capable of protecting against any diseases. Thus, for this reason as well, Thorns does not anticipate claims 29, 30, and 56.

Ground of rejection 3

Are claims 1, 3-12, and 29-56 obvious over Boothby I in view of Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat) and Thorns?

Claims 1, 3-12, and 29-56 have been rejected as being obvious over Boothby I in view of Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat) and Thorns. These claims do not stand or fall together, but instead should be grouped according to the subheadings below.

Claims 1, 3-12, and 29-56 (all of the claims subject to this rejection)

As discussed above, the presently claimed vaccine does not cause unfavorable reactions. As discussed above, this limitation is lacking in Boothby I and Thorns, since the *M. bovis* in Boothby I caused hypersensitivity and the *M. bovis* in Thorns caused histopathological changes. Thus, these two publications lack a disclosure of this claim limitation.

As explained more fully below, Poumarat did not disclose vaccines of any kind, and thus failed to teach or suggest a vaccine that does not cause unfavorable reactions.

In view of the complete lack of disclosure of this limitation in the prior art, no combination of the cited references can possibly disclose or suggest this limitation, and the Appellants thus submit that a *prima facie* case of obviousness for claims 1, 3-12, and 29-56 has not been and cannot be made.

Claims 8-12, 31-39, and 46-51

Claims 8-12, 31-39, and 46-51 recite "at least two" *M. bovis* biotypes.

Boothby I does not disclose a vaccine that contains more than one biotype. Even if Thorns is viewed as disclosing vaccines (which the Appellants dispute), Thorns still does not disclose a vaccine containing more than one biotype since all the strains in Thorns were administered individually.

Poumarat does not disclose any vaccines since Poumarat is limited to a study of the antigenic characteristics of certain strains of *Mycoplasma bovis*. Moreover, Poumarat discourages, and thus teaches away from, the use of more than one biotype.

Poumarat divided *Mycoplasma bovis* isolates into 13 different "genomic groups." Poumarat then looked at the antigenic variability between and among these genomic groups. Although Poumarat found much antigenic variability, this variability did not correlate with membership in any particular genomic group. In other words, the same amount of antigenic variability could be found within groups as between groups. See page 318, 2nd paragraph:

> Antigenic profiles of the *M. bovis* strains obtained by immunoblotting with J008 calf serum differed markedly one from the other, the heterogeneity being equally great among strains belonging to the same genomic group and those coming from different genomic groups. There appeared to be no relation between the genomic variability of *M. bovis* and the antigenic variability ...

Because Poumarat teaches that antigenic variability is as great within *Mycoplasma bovis* groups as across *Mycoplasma bovis* groups, Poumarat teaches that there would be no gain in antigenic variability from including more than one type of *Mycoplasma bovis* in a vaccine. That is, there would be no point in having more than one type of *Mycoplasma bovis* in a vaccine. Poumarat thus discourages one of ordinary skill in the art from including more than one biotype in a vaccine, and thus teaches away from the invention defined by claims 8-12, 31-39, and 46-51.

"A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998).

Claims 34-39 and 46-51

Poumarat's teaching away from a vaccine containing more than one biotype is especially pertinent in connection with claims 34-39 and 46-51. These claims all require that the at least two biotypes be genetically different, as judged by analysis of DNA or RNA. Poumarat expressly teaches that such genetic differences are irrelevant with respect to antigenicity since Poumarat teaches that there appears to be "no relation between the genomic variability of *M. bovis* and the antigenic variability." One of ordinary skill in the art would clearly interpret this conclusion as a teaching that nothing is to be gained from including biotypes that are genetically different in a vaccine, and thus would be discouraged from the invention of claims 34-39 and 46-51. Such a distinct teaching away from the Appellants' invention in the prior art constitutes a strong indication of non-obviousness, and *a fortiori* negates any possible case of *prima facie* obviousness.

Claims 29, 30, and 40-45

Claims 29, 30, and 40-45 recite that the vaccine is "protective against *Mycoplasma bovis* mastitis."

None of Boothby I, Thorns, or Poumarat disclose or suggest this limitation.

Furthermore, there was a long-felt need in the art for an effective vaccine against bovine mastitis. See, e.g., Hanson, (September, 2001) Bovine Veterinarian 4-8 (Hanson I) and Hanson, (October, 2001) Bovine Veterinarian 12-20 (Hanson II), which contain extensive descriptions of the problems caused by bovine mastitis and the difficulty of dealing with this disease. For example, Hanson I quotes a veterinarian as follows (page 4):

> "*Mycoplasma* mastitis is a doubly insulting disease," says Blackmer. "Not only can it be remarkably contagious when it is present but it absolutely does not respond to antibiotic therapy. In fact, treatment can actually cause epidemics, because it frequently is spread by unsound intramammary therapy practices."

The art also discloses that others tried and failed to produce a vaccine protective against mastitis. Boothby et al., 1986, Can. J. Vet. Res. 50:200-204 (Boothby II) shows this failure of others, and also teaches away from the present claims. Boothby II tested whether killed *M. bovis* would be effective as a vaccine against bovine mastitis and found that it was not. Despite their prior exposure to killed *M. bovis*, the treated cows in Boothby II were not protected against infection (see page 202, middle column: "All experimentally challenged quarters became infected ..."). Thus, Boothby II was unsuccessful. Such a failure is a clear and strong deterrent to others. The skilled person therefore would undoubtedly have been deterred and discouraged by Boothby II from attempting to produce *M. bovis* vaccine, and thus would not even have sought the solution provided by the Appellants.

Moreover, the treated animals in Boothby II showed poorer milk production than the untreated animals. The treated cows suffered significant and persistent reductions in the level of milk production. The control cows exhibited a smaller and more transient drop in milk production. See Figure 2 on page 202 for a comparison of treated and control cows. Thus, not only did the killed *M. bovis* fail to protect the treated cows, but

it caused milk production to be even worse than it would have been had the cows not been treated. Since the primary purpose for having dairy herds is to produce milk, one of ordinary skill in the art would certainly be deterred by a result that decreased the production of milk.[3] Given that Boothby would have deterred the skilled person in two major respects - lack of efficacy and decrease in milk production - Boothby must be seen as teaching away from the Appellants' invention.

Claim 56

Claim 56 is directed to attenuated vaccines that are protective against respiratory pneumonia.

Boothby I and Poumarat do not disclose attenuated *Mycoplasma bovis*. As discussed above, although Thorns does disclose attenuated strains of *Mycoplasma bovis*, Thorns states that these strains are not vaccines, but might provide "further insight" which could "perhaps" lead to the development of a vaccine. See Thorns, page 332, right column, 3rd paragraph:

> Whatever mechanisms the virulent strains have lost or modified, they should provide further insight into the pathogenesis of *M. bovis* mastitis which could perhaps lead to a stable vaccine for this disease. [emphasis added]

Given the lack of disclosure of an attenuated vaccine that is protective against respiratory pneumonia in any of Boothby I, Thorns, or Poumarat, and the lack of any suggestion as to how such a vaccine could be produced in those references, it cannot properly be said that those references make obvious claim 56.

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[3] This is recognized by Boothby II at page 200, right column, where it is stated: "If prophylactic vaccination is to be efficacious, it must have minimal effects on the health and productive capabilities of

CONCLUSION

For the reasons discussed above, the Appellants respectfully request that the Board of Patent Appeals and Interferences reverse:

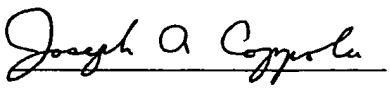
(1) the rejection of claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55 as anticipated under 35 U.S.C. §102(b) by Boothby, Immunologic Responses to Mycoplasma bovis, University Microfilm International (Dissertation) 1-172, 1982 (Boothby I);

(2) the rejection of claims 1, 4, 5, 7, 29, 30, and 56 as anticipated under 35 U.S.C. §102(b) by Thorns et al., 1980, Res. Vet. Sci. 29:328-332 (Thorns); and

(3) the rejection of claims 1, 3-12, and 29-56 as obvious under 35 U.S.C. §103(a) over Boothby I in view of Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat) and Thorns.

Respectfully submitted,

Dated: MAY 22, 2006



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the cow."

CLAIMS APPENDIX

1. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, and wherein the adjuvant does not include saponin and the clinical disease includes respiratory pneumonia.

2. canceled

3. The vaccine of claim 1, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each inactivated biotype is at least 10^8 *M.* bovis cells.

4. The vaccine of claim 1, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

5. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A, biotype B and Biotype C, and wherein the adjuvant does not include saponin.

6. The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each selected inactivated *Mycoplasma bovis* biotype is at least 10^8 *M. bovis* cells.

7. The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each selected attenuated *Mycoplasma bovis* biotype is at least 10^5 *M. bovis* cells.

8. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least two inactivated or attenuated *Mycoplasma bovis* biotypes and a pharmaceutically acceptable excipient.

9. The vaccine of claim 8, further comprising a suitable adjuvant.

10. The vaccine of claim 8, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each inactivated biotype is at least 10^8 *M. bovis* cells.

11. The vaccine of claim 8, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

12. The vaccine of claim 8, wherein the *Mycoplasma bovis* biotypes are selected from the group consisting of biotype A, biotype B and biotype C.

13-28. (canceled)

29. A vaccine which is protective against *Mycoplasma bovis* mastitis in a bovine species comprising at least one inactivated or attenuated Mycoplasma *bovis* biotype and a pharmaceutically acceptable excipient.

30. The vaccine of claim 29, where the vaccine is protective against *Mycoplasma bovis* mastitis in a bovine species following systemic administration.

31. The vaccine of claim 30, comprising at least two inactivated *Mycoplasma bovis* biotypes.

32. The vaccine of claim 31, wherein the vaccine includes at least one inactivated *Mycoplasma bovis* biotype selected from the group consisting of biotype A, biotype B and biotype C.

33. The vaccine of claim 31 wherein the vaccine contains approximately 10^8 cells of each biotype in a volume of 2-5 milliliters.

34. The vaccine of claim 8 wherein the at least two inactivated or attenuated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

35. The vaccine of claim 34 wherein the analysis is by PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

36. The vaccine of claim 35 wherein the analysis is by PCR fingerprinting.

37. The vaccine of claim 36 wherein the PCR fingerprinting uses arbitrarily chosen primers.

38. The vaccine of claim 37 wherein the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

39. The vaccine of claim 8 wherein the at least two *Mycoplasma bovis* biotypes have been identified as being different biotypes by a process comprising:
(a) isolating DNA from the biotypes;
(b) amplifying the DNA by PCR;
(c) separating the amplified DNA by gel electrophoresis; and
(d) comparing the resulting patterns from the gel electrophoresis to identify the different biotypes.

40. The vaccine of claim 30 wherein, when the vaccine is administered to a plurality of cows in a herd of cows, the incidence of mastitis caused by *Mycoplasma bovis* in the herd before administering is greater than the incidence of mastitis caused by *Mycoplasma bovis* in the herd after administering.

41. The vaccine of claim 40 wherein the vaccine is administered to at least about 50% of the herd.

42. The vaccine of claim 41 where the vaccine is administered together with an adjuvant.

43. The vaccine of claim 42 wherein the adjuvant is an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; incomplete Freund's adjuvant; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; saponin; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; paraffin oil; or muramyl dipeptide.

44. The vaccine of claim 30 where the *Mycoplasma bovis* biotype is inactivated and has been inactivated by treatment with: formalin, azide, freeze-thawing, sonication, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal, or binary ethyleneimine.

45. The vaccine of claim 44 where the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone.

46. The vaccine of claim 31 wherein the at least two inactivated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

47. The vaccine of claim 46 wherein the analysis is by PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

48. The vaccine of claim 47 wherein the analysis is by PCR fingerprinting.

49. The vaccine of claim 48 wherein the PCR fingerprinting uses arbitrarily chosen primers.

50. The vaccine of claim 49 wherein the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

51. The vaccine of claim 31 wherein the at least two *Mycoplasma bovis* biotypes have been identified as being different biotypes by a process comprising:
(a) isolating DNA from the biotypes;
(b) amplifying the DNA by PCR;
(c) separating the amplified DNA by gel electrophoresis; and
(d) comparing the resulting patterns from the gel electrophoresis to identify the different biotypes.

52. A whole-cell vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and an adjuvant selected from the group consisting of: an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; and paraffin oil.

53. The vaccine of claim l, wherein the *Mycoplasma bovis* biotype is inactivated.

54. The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is inactivated.

55. The vaccine of claim 52, wherein the *Mycoplasma bovis* biotype is inactivated.

56. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one attenuated *Mycoplasma bovis* biotype and a

pharmaceutically acceptable excipient, wherein the clinical disease includes respiratory pneumonia.

Evidence Appendix

The evidence relied upon, and where in the record that evidence was entered, is as follows:

1. Boothby, Immunologic Responses to Mycoplasma bovis, University Microfilm International (Dissertation) 1-172, 1982 (Boothby I). Boothby I was applied by the Examiner in an anticipation rejection in the Office Action dated May 25, 2005, bottom of page 2 to middle of page 5.
2. Heller et al., 1993, Vet. Microbiol. 37:127-133 (Heller). Heller was submitted in an Information Disclosure Statement filed April 16, 2002. The Examiner returned a copy of the PTO-1449 Form accompanying this Information Disclosure Statement, with the entry for this publication initialed, with the Office Action dated September 30, 2003.
3. Hanson, (September, 2001) Bovine Veterinarian 4-8 (Hanson I). Hanson I was submitted in an Information Disclosure Statement filed April 16, 2002. The Examiner returned a copy of the PTO-1449 Form accompanying this Information Disclosure Statement, with the entry for this publication initialed, with the Office Action dated September 30, 2003.
4. Hanson, (October, 2001) Bovine Veterinarian 12-20 (Hanson II). Hanson II was submitted in an Information Disclosure Statement filed April 16, 2002. The Examiner returned a copy of the PTO-1449 Form accompanying this Information Disclosure Statement, with the entry for this publication initialed, with the Office Action dated September 30, 2003.

5. *Ex parte Hervy A. Morris* (available in the Westlaw database at 1998 WL 1736155), a copy of which is enclosed herewith since this is a decision of the Board of Patent Appeals & Interferences that has not been published in a West reporter or in United States Patents Quarterly.
6. Thorns et al., 1980, Res. Vet. Sci. 29:328-332 (Thorns). Thorns was applied by the Examiner in an anticipation rejection in the Office Action dated May 25, 2005, middle of page 5 to middle of page 7.
7. Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat). Poumarat was applied by the Examiner in an anticipation rejection in the Office Action dated May 25, 2005, middle of page 7 to top of page 12.
8. Boothby et al., 1986, Can. J. Vet. Res. 50:200-204 (Boothby II). Boothby II was submitted in an Information Disclosure Statement filed April 16, 2002. The Examiner returned a copy of the PTO-1449 Form accompanying this Information Disclosure Statement, with the entry for this publication initialed, with the Office Action dated September 30, 2003.

Related Proceedings Appendix

(none)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Leonard et al.
SERIAL NO.	:	09/708,352
FILING DATE	:	November 8, 2000
FOR	:	VACCINES FOR MYCOPLASMA BOVIS AND METHODS OF USE
EXAMINER	:	Ford
GROUP ART UNIT:		1645

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: March 29, 2004 Reg. No. 38,413

Joseph A. Coppola

AMENDMENT

Sir:

In response to the Office Action dated September 30, 2003, please consider the following amendments and remarks. Enclosed herewith is a Petition for the Extension of Time for a period sufficient to permit the filings of this response.

CLAIM AMENDMENTS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (currently amended) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, and wherein the ~~vaccine~~ adjuvant does not include saponin and the clinical disease includes respiratory pneumonia.

2. canceled

3. (currently amended) The vaccine of claim 1, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each inactivated biotype is at least 10^8 *M.* bovis cells.

4. (currently amended) The vaccine of claim 1, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

5. (currently amended) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A, biotype B and Biotype C, and wherein the ~~vaccine~~ adjuvant does not include saponin.

6. (currently amended) The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each selected inactivated *Mycoplasma bovis* biotype is at least 10^8 *M. bovis* cells.

7. (currently amended) The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each selected attenuated *Mycoplasma bovis* biotype is at least 10^5 *M. bovis* cells.

8. (currently amended) ~~The vaccine of claim 1, wherein the~~ A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least two inactivated or attenuated *Mycoplasma bovis* biotypes and a pharmaceutically acceptable excipient.

9. (original) The vaccine of claim 8, further comprising a suitable adjuvant.

10. (currently amended) The vaccine of claim 8, wherein the *Mycoplasma bovis* biotype is inactivated and the amount of each inactivated biotype is at least 10^8 *M. bovis* cells.

11. (currently amended) The vaccine of claim 8, wherein the *Mycoplasma bovis* biotype is attenuated and the amount of each attenuated biotype is at least 10^5 *M. bovis* cells.

12. (currently amended) The vaccine of claim 8, wherein the *Mycoplasma bovis* ~~biotype is~~ biotypes are selected from the group consisting of biotype A, biotype B and biotype C.

13-28. (canceled)

29. (new) A vaccine which is protective against *Mycoplasma bovis* mastitis in a bovine species comprising at least one inactivated or attenuated Mycoplasma *bovis* biotype and a pharmaceutically acceptable excipient.

30. (new) The vaccine of claim 29, where the vaccine is protective against *Mycoplasma bovis* mastitis in a bovine species following systemic administration.

31. (new) The vaccine of claim 30, comprising at least two inactivated *Mycoplasma bovis* biotypes.

32. (new) The vaccine of claim 31, wherein the vaccine includes at least one inactivated *Mycoplasma bovis* biotype selected from the group consisting of biotype A, biotype B and biotype C.

33. (new) The vaccine of claim 31 wherein the vaccine contains approximately 10^8 cells of each biotype in a volume of 2-5 milliliters.

34. (new) The vaccine of claim 8 wherein the at least two inactivated or attenuated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

35. (new) The vaccine of claim 34 wherein the analysis is by PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

36. (new) The vaccine of claim 35 wherein the analysis is by PCR fingerprinting.

37. (new) The vaccine of claim 36 wherein the PCR fingerprinting uses arbitrarily chosen primers.

38. (new) The vaccine of claim 37 wherein the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

39. (new) The vaccine of claim 8 wherein the at least two *Mycoplasma bovis* biotypes have been identified as being different biotypes by a process comprising:
(a) isolating DNA from the biotypes;
(b) amplifying the DNA by PCR;

(c) separating the amplified DNA by gel electrophoresis; and
(d) comparing the resulting patterns from the gel electrophoresis to identify the different biotypes.

40. (new) The vaccine of claim 30 wherein, when the vaccine is administered to a plurality of cows in a herd of cows, the incidence of mastitis caused by *Mycoplasma bovis* in the herd before administering is greater than the incidence of mastitis caused by *Mycoplasma bovis* in the herd after administering.

41. (new) The vaccine of claim 40 wherein the vaccine is administered to at least about 50% of the herd.

42. (new) The vaccine of claim 41 where the vaccine is administered together with an adjuvant.

43. (new) The vaccine of claim 42 wherein the adjuvant is an aluminum hydroxide-oil emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; incomplete Freund's adjuvant; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; saponin; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; paraffin oil; or muramyl dipeptide.

44. (new) The vaccine of claim 30 where the *Mycoplasma bovis* biotype is inactivated and has been inactivated by treatment with: formalin, azide, freeze-thawing, sonication, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal, or binary ethyleneimine.

45. (new) The vaccine of claim 44 where the *Mycoplasma bovis* biotype has been inactivated by treatment with β-propiolactone.

46. (new) The vaccine of claim 31 wherein the at least two inactivated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes.

47. (new) The vaccine of claim 46 wherein the analysis is by PCR fingerprinting, analysis of ribosomal RNA, or analysis of DNA polymorphisms.

48. (new) The vaccine of claim 47 wherein the analysis is by PCR fingerprinting.

49. (new) The vaccine of claim 48 wherein the PCR fingerprinting uses arbitrarily chosen primers.

50. (new) The vaccine of claim 49 wherein the PCR fingerprinting uses as primers 5' NNN NCG NCG NCA TCN GGC 3' (SEQ ID NO:1) and 5' NCG NCT TAT CNG GCC TAC 3' (SEQ ID NO:2).

51. (new) The vaccine of claim 31 wherein the at least two *Mycoplasma bovis* biotypes have been identified as being different biotypes by a process comprising:
(a) isolating DNA from the biotypes;
(b) amplifying the DNA by PCR;
(c) separating the amplified DNA by gel electrophoresis; and
(d) comparing the resulting patterns from the gel electrophoresis to identify the different biotypes.

52. (new) A whole-cell vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and an adjuvant selected from the group consisting of: an aluminum hydroxide-oil

emulsion; a mineral, vegetable, or fish oil-water emulsion; a water-oil-water emulsion; *E. coli* J5; dextran sulfate; iron oxide; sodium alginate; Bacto-Adjuvant; a synthetic polymer; Carbopol; a poly-amino acid; a co-polymer of amino acids; carrageenan; REGRESSIN®; N, N-dioctadecyl-N'-N'-bis(2-hydroxyethyl) propanediamine; a long chain polydispersed β(1,4) linked mannan polymer interspersed with O-acetylated groups; deproteinized cell wall extracts from a non-pathogenic strain of *Mycobacterium*; mannite monooleate; and paraffin oil.

53. (new) The vaccine of claim 1, wherein the *Mycoplasma bovis* biotype is inactivated.

54. (new) The vaccine of claim 5, wherein the *Mycoplasma bovis* biotype is inactivated.

55. (new) The vaccine of claim 52, wherein the *Mycoplasma bovis* biotype is inactivated.

56. (new) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient, wherein the clinical disease includes respiratory pneumonia.

Remarks

Prior to this Amendment, claims 1-22, 24, and 27 were pending. By this Amendment, claims 2, 13-22, 24, and 27 have been canceled without prejudice to the Applicants' right to prosecute these claims in continuing applications. New claims 29-56 have been added. Therefore, following entry of this Amendment, claims 1, 3-12, and 29-56 will be pending.

Claims 1, 3-8, and 10-12 have been amended herein. Support for these amendments is found in the specification as follows:

Claim 1 has been amended to recite that the adjuvant does not include saponin. Support for this recitation is found in the specification at page 8, lines 7-26, especially line 21. Claim 1 has been amended to recite that the clinical disease includes respiratory pneumonia. Support for this recitation is found in the specification at Example 7, page 21, line 27 to page 22, line 22 and the abstract.

Claim 3 has been amended to clarify that the *Mycoplasma bovis* biotype is inactivated. Support for this amendment is found in the specification at page 4, lines 6-19.

Claim 4 has been amended to clarify that the *Mycoplasma bovis* biotype is attenuated. Support for this amendment is found in the specification at page 4, lines 21-29.

Claim 5 has been amended to recite that the vaccine includes an adjuvant that does not contain saponin. Support for this recitation is found in the specification at page 8, lines 7-26, especially line 21.

Claim 6 has been amended to clarify that the *Mycoplasma bovis* biotype is inactivated. Support for this amendment is found in the specification at page 4, lines 6-19.

Claim 7 has been amended to clarify that the *Mycoplasma bovis* biotype is attenuated. Support for this amendment is found in the specification at page 4, lines 21-29.

Claim 8 has been amended to place it into independent form.

Claim 10 has been amended to clarify that the *Mycoplasma bovis* biotype is inactivated. Support for this amendment is found in the specification at page 4, lines 6-19.

Claim 11 has been amended to clarify that the *Mycoplasma bovis* biotype is attenuated.

Support for this amendment is found in the specification at page 4, lines 21-29.

Claim 12 has been amended merely to correct its grammar.

Support for new claims 29-56 is found in the application as follows:

Support for new claim 29 is found in the specification at page 18, line 24 to page 20, line 17; at page 20, line 20 to page 21, line 25 (see in particular page 21, lines 11-15); at page 22, line 24 to page 23, line 3 (see in particular page 22, lines 29-31); at page 23, lines 5-15 (see in particular page 23, lines 13-14).

Support for new claim 30 is found in the specification at page 9, line 6.

Support for new claim 31 is found in the specification at page 5, lines 23-25 and page 9, lines 1-2.

Support for new claim 32 is found in the specification at page 5, lines 22-23.

Support for new claim 33 is found in the specification at page 10, line 5 and page 10, line 8.

Support for new claim 34 is found in the specification at page 5, lines 12-13, Figures 1 and 2.

Support for new claim 35 is found in the specification at page 12, lines 6-28; Figures 1 and 2; and page 5, line 13.

Support for new claim 36 is found in the specification at page 12, line 4 to page 14, line 13.

Support for new claim 37 is found in the specification at page 12, line 10.

Support for new claim 38 is found in the specification at page 12, lines 13-14.

Support for new claim 39 is found in the specification at page 12, lines 15-28; and Figures 1 and 2.

Support for new claim 40 is found in the specification at page 18, line 24 to page 19, line 31.

Support for new claim 41 is found in the specification at page 23, lines 1-2.

Support for new claim 42 is found in the specification at page 8, lines 7-8.

Support for new claim 43 is found in the specification at page 8, lines 16-26 and page 11, lines 3-4. A water-oil-water emulsion is disclosed at Example 2, part D ("Adjuvanting

and Formulation of Vaccine"), page 17, lines 17-19, where in step 7 it is disclosed that an oil adjuvant is added to the inactivated *M. bovis* so as to produce a vaccine with 4% to 12% oil. One skilled in the art would understand that such a low amount of oil in the vaccine would not be enough to completely surround the aqueous phase of the vaccine and thus one skilled in the art would understand this passage to be a disclosure of an water-oil-water emulsion.

Support for new claim 44 is found in the specification at page 4, lines 13-17.

Support for new claim 45 is found in the specification at page 4, lines 17-19 and page 16, lines 22-28.

Support for new claim 46 is found in the specification at page 5, lines 12-13, Figures 1 and 2.

Support for new claim 47 is found in the specification at page 12, lines 6-28; Figures 1 and 2; and page 5, line 13.

Support for new claim 48 is found in the specification at page 12, line 4 to page 14, line 13.

Support for new claim 49 is found in the specification at page 12, line 10.

Support for new claim 50 is found in the specification at page 12, lines 13-14.

Support for new claim 51 is found in the specification at page 12, lines 15-28; and Figures 1 and 2.

Support for new claim 52 with respect to the recitation of adjuvants is found in the specification at page 8, lines 16-26 and page 11, lines 3-4. A water-oil-water emulsion is disclosed at Example 2, part D ("Adjuvanting and Formulation of Vaccine"), page 17, lines 17-19, where in step 7 it is disclosed that an oil adjuvant is added to the inactivated *M. bovis* so as to produce a vaccine with 4% to 12% oil. One skilled in the art would understand that such a low amount of oil in the vaccine would not be enough to completely surround the aqueous phase of the vaccine and thus one skilled in the art would understand this passage to be a disclosure of an water-oil-water emulsion. Support for new claim 51 with respect to the recitation of a "whole-cell" vaccine is found in the specification at page 16, lines 22-28. While the phrase "whole-cell" does not appear in this portion of the specification, it would be clear to one skilled in the art that the vaccine described in this portion of the specification is a

whole-cell vaccine. This is because the process of preparing a vaccine described in this portion begins with whole *Mycoplasma bovis* cells in culture (see page 16, line 23) and there are no steps described in which components of the whole cells are fractionated, and at the end of the process "cells" are concentrated for use as a vaccine (see page 16, lines 27-28). Further support is found at page 9, lines 27-28, which makes clear that the vaccine can comprise either whole-cells of *Mycoplasma bovis* ("inactivated or attenuated M. bovis biotypes") or non-whole-cell portions of *Mycoplasma bovis* ("or a portion thereof").

Support for new claim 53 is found in the specification at page 4, lines 6-19.

Support for new claim 54 is found in the specification at page 4, lines 6-19.

Support for new claim 55 is found in the specification at page 4, lines 6-19.

Support for new claim 56 is found in the specification at at Example 7, page 21, line 27 to page 22, line 22 and the abstract.

Claim objections

Claims 8 and 22 were objected to as being substantial duplicates of one another.

The Applicants respectfully disagree but, in the interests of expediting prosecution, claim 22 has been canceled. Thus, it is submitted that this objection is now moot.

Claim 21 was objected to for failing to further limit the subject matter of claim 1, from which claim 21 depends.

The Applicants respectfully disagree but, in the interests of expediting prosecution, claim 21 has been canceled. Thus, it is submitted that this objection is now moot.

The rejections under 35 U.S.C. §112

Claims 1-12, 21-22, 24, and 27 were rejected for lack of written description due to the recitation of "wherein the vaccine does not include saponin."

The Examiner stated that this recitation contained new matter since it required that the vaccine as a whole not include saponin rather than that the adjuvant not include saponin. See the Office Action, at page 4, lines 3-8:

It should be noted that saponin can be used as an adjuvant or it can be used as a detergent. The concepts are different. Therefore, a composition that does not contain saponin is different from a composition that does not comprise saponin as an adjuvant. The "new genus" in which the vaccine per se, rather than adjuvant component as saponin is the excluded material is not supported by the original disclosure.

Claim 1 has been amended to recite that the adjuvant does not include saponin. Claim 2 has been canceled. Claims 3 and 4 depend from claim 1. Claim 5 has been amended so that it no longer recites saponin. Claims 6 and 7 depend from claim 5. Claim 8 has been amended to place it into independent form and in this form no longer recites saponin. Claims 9-12 depend from claim 8. Claims 21, 22, 24, and 27 have been canceled. Thus, the only claims that recite that any component of the vaccine does not include saponin are claims 1, 3, and 4, and those claims now recite that the adjuvant does not include saponin. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Claims 8-12, 21-22, and 24 were rejected as being indefinite.

Claim 8 was rejected because "it is not clear as to whether there are one or two pharmaceutically acceptable excipients included in the vaccine composition." Claim 8 has been amended so as to obviate this rejection by making it clear that there is only one pharmaceutically acceptable excipient required. Therefore, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-12, 21-22, 24, and 27 were rejected as being indefinite. The Examiner stated that it is not clear what is being referred to by the word "biotypes."

The Applicants respectfully traverse this rejection. The specification provides an explicit definition of "biotype" as being a variant that can be distinguished by one or more characteristics. In addition, the specification provides examples of the kinds of characteristics that can be used to distinguish biotypes and provides citations to literature

that provide teachings with regard to techniques that can be used to distinguish biotypes See page 5, lines 11-18:

> The term "biotype" means a variant of a species, i.e. a strain, that can be distinguished by one or more characteristics, such as ribosomal RNA sequence variation, DNA polymorphisms, serological typing, or toxin production (*see e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989; *DNA cloning: A Practical Approach*, Volumes I and II, Glover, D.M. ed., IRL Press Limited, Oxford, 1985; Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Publications, N.Y. (1988)).

The specification also provides working examples of how three different biotypes can be distinguished. See Figures 1 and 2 and the accompanying descriptive text at pages 3 and 12-14 , wherein biotypes A, B, and C are described.

It is well settled that the definiteness of a claim is not to be judged in a vacuum. Instead the claim must be viewed in the context of the disclosure of the application from which it is derived. The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986). See also BJ Services Co. v. Halliburton Energy Services, Inc., 338 F.3d 1368, 1372, 67 USPQ2d 1692, (Fed. Cir. 2003): "The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification."

Given the explicit teachings of the specification referred to above with respect to the meaning of biotypes, the Applicants submit that this word would be clearly understood by one skilled in the art, upon reading the specification.

The rejections under 35 U.S.C. §102(b)

Claims 1, 3, 5-6, 21, 24, and 27 were rejected as being anticipated by Boothby, *Immunologic Responses to Mycoplasma bovis*, University Microfilm International (Dissertation) 1-172, 1982 (Boothby). The Examiner stated that the Applicants must show "that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine" (Office Action, page 7, 3rd paragraph).

The Applicants respectfully traverse this rejection. There is a clear functional difference between the Applicants' vaccine and Boothby's. This indicates that Boothby's vaccine and the Applicants' vaccine are not the same.

The vaccine of the present invention does not cause unfavorable or adverse reactions. See the specification, at page 23, lines 2-3: "No unfavorable reactions resulting from the vaccine's use have been reported;" page 23, lines 14-15: "No unfavorable reactions in animals receiving the product have been reported;" page 20, line 1: "No injection reactions were observed;" and the abstract: "These vaccines demonstrate no undesirable side effects ..."

In contrast, Boothby's vaccine produces a very unfavorable reaction - all of Boothby's animals showed hypersensitivity (see Boothby, page 136, 3rd paragraph). This is a real functional difference between the Applicants' vaccine and Boothby's that must be due to the nature of the vaccine, and cannot be attributed to any "intended use" of the vaccine.

Case law holds that vaccines can be patentable over prior art based on functional characteristics. See Ex parte Plotkin, 174 USPQ 39 (Pat. Off. Bd. App. 1971). In Plotkin, the claimed vaccine had the functional characteristic of being able to be administered intranasally with high effectiveness. This was found to confer patentability to claims to the vaccine itself over the prior art.

Moreover claim 5 and dependent claim 6 therefrom require that the vaccine comprises particular biotypes that are not disclosed in Boothby. Claims 21, 24, and 27 have been canceled.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The Applicants submit that the new claims are not anticipated by Boothby for the same reasons as discussed above with respect to claims 1, 3, 5-6, 21, 24, and 27 as well as for the additional reasons that are discussed below.

New independent claim 29 recites that the vaccine "is protective against *Mycoplasma bovis* mastitis in a bovine species." This recitation makes clear that the functional characteristic of being protective against mastitis is not simply an intended use but rather is a characteristic of the vaccine itself. This characteristic distinguishes over the prior art, such as the vaccine disclosed in Boothby. Given that the vaccine in Boothby clearly differs from the Applicants' vaccine (as shown by differences with respect to causing unfavorable reactions), it cannot be assumed that Boothby's vaccine is protective against mastitis.

Furthermore, publications later than Boothby indicate that Boothby could not have disclosed a vaccine protective against mastitis. For example, Heller et al., 1993, Vet. Microbiol. 37:127-133[1] did not mention that one should vaccinate to control mastitis but instead stated that culling is necessary. See page 127: "To control the spread of this disease, an early detection of the pathogen is crucial since the removal and culling of infected cows is necessary to prevent fresh infections." In Hanson, (September, 2001) Bovine Veterinarian 4-8[2] and Hanson, (October, 2001) Bovine Veterinarian 12-20[3],

[1] Reference A32 of the Information Disclosure Statement filed April 16, 2002.

[2] Reference A30 of the Information Disclosure Statement filed April 16, 2002.

[3] Reference A31 of the Information Disclosure Statement filed April 16, 2002.

methods to prevent mastitis or mitigate its effects are described but the methods do not include vaccination, indicating that no effective vaccine was known to the art.

New claims 30-33 and 40-51 depend from new claim 29 and thus the same considerations apply to these dependent claims.

New claims 34-39 depend from claim 8, which recites "at least two inactivated or attenuated *Mycoplasma bovis* biotypes." Since Boothby does not disclose a vaccine comprising more than a single biotype, Boothby does not anticipate these new claims.

New independent claim 52 recites that the vaccine comprises an adjuvant that differs from the adjuvants listed in Boothby.[4] Therefore, Boothby does not anticipate new claim 52. New claim 55 depends from new claim 52 and therefore Boothby does not anticipate new claim 55 either.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Claims 1, 4, 5, and 7 were rejected as being anticipated by Thorns et al., 1980, Res. Vet. Sci. 29:328-332 (Thorns).

The Applicants respectfully traverse this rejection. All of the rejected claims are directed to vaccines that are protective against diseases caused by *Mycoplasma bovis* in bovines. Thorns does not disclose a vaccine. Thorns discloses attenuated strains of *Mycoplasma bovis* that were injected into mice. There is no disclosure in Thorns that the attenuated strains were protective against any disease in the injected mice. Thorns does not

[4] At page 131, Boothby discloses the use of the following adjuvants:
Freund's incomplete adjuvant
N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP)
Amphotericin B
Combined magnesium/aluminum hydroxide
Killed *Bordatella pertussis*

even disclose any data that indicate the attenuated strains caused any stimulation of the immune systems of the mice against *Mycoplasma bovis.*

On pages 7 and 8 of the Office Action, the Examiner stated that the highly passaged strains in Thorns did not cause a systemic response, inflammation, or abnormal glands. The Applicants wish to point out that these responses (or lack thereof) were due to the injected strains themselves. In other words, Thorns showed that highly passaged strains were attenuated in the sense that they did not cause those responses to the same degree as low passaged strains. This is not the same as, nor is it predictive of, a showing that these attenuated strains could function as vaccines, to protect against disease caused by later exposure to *Mycoplasma bovis*. Thorns provided no evidence on that point. In particular, Thorns provided no evidence that the mice that were given the attenuated strains were protected from disease when later challenged with *Mycoplasma bovis*. Apparently, Thorns did not even challenge the mice.

Moreover, the authors of Thorns did not consider that their strains were vaccines. The authors considered that the work they disclosed provided information and a starting point for research that might someday perhaps lead to the production of a vaccine against *Mycoplasma bovis*. See page 332, right column, 3rd paragraph:

> Whatever mechanisms the virulent strains have lost or modified, they should provide further insight into the pathogenesis of *M. bovis* mastitis which could perhaps lead to a stable vaccine for this disease. [emphasis added]

The last phrase of this sentence makes clear that the authors of Thorns did not think that they have already provided such a vaccine.

Furthermore, Thorns is completely silent on the subject of inactivated, as opposed to attenuated, vaccines. Therefore, for this reason also, Thorns does not anticipate claims 3, 6, 10, 31-33, 44-51, and 53-55, which require an inactivated vaccine.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §103(a)

Claims 1-12, 21-22, 24, and 27 were rejected as being obvious over Boothby in view of Poumarat et al., 1994, Vet. Microbiol. 40:305-321 (Poumarat) and Thorns.

As discussed above, Boothby does not disclose a vaccine that does not cause unfavorable reactions or a vaccine that is protective against mastitis. Neither Thorns nor Poumarat provide this subject matter that is missing in Boothby. Thorns does not disclose vaccines, and certainly not vaccines that do not cause unfavorable reactions[5] or vaccines that are protective against mastitis.[6] Poumarat also does not disclose any vaccines since Poumarat is limited to a study of the antigenic characteristics of certain strains of *Mycoplasma bovis*.

Thorns and Poumarat do not contain the subject matter that is missing from Boothby, nor suggest how to obtain such subject matter. There is no teaching in Thorns or Poumarat that would enable one skilled in the art to produce a vaccine that does not cause unfavorable reactions. Therefore, one of ordinary skill in the art could not arrive at the present invention by combining Thorns and Poumarat with Boothby. Accordingly, all of the present claims are non-obvious over Boothby, Poumarat, and Thorns, and it is respectfully requested that this rejection be withdrawn.

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[5] All of the strains in Thorns caused some kind of histopathological changes, albeit some strains only caused minor changes. See the last sentence of the abstract: "the high passage strains produced only minor histopathological changes." See also the right column in Table 1 on page 329, which shows that only the control (i.e., no *Mycoplasma bovis*) injections resulted in no histopathological changes. Thus, even if Thorns disclosed vaccines, which the Applicants dispute, Thorns would not disclose vaccines that have the same functional characteristics as the Applicants' vaccine.

[6] As discussed above, Thorns provided absolutely no evidence that the strains used protected against any disease.

With respect to claims 8-12, 31-39, and 46-51, which require two or more biotypes, the Applicants wish to point out that Poumarat contradicts the Examiner's argument and teaches away from the claimed subject matter.

Poumarat divided *Mycoplasma bovis* isolates into 13 different "genomic groups." Poumarat then looked at the antigenic variability between and among these genomic groups. Although Poumarat found much antigenic variability, this variability did not correlate with membership in any particular genomic group. In other words, the same amount of antigenic variability could be found within groups as between groups. See page 318, 2nd paragraph:

> Antigenic profiles of the *M. bovis* strains obtained by immunoblotting with J008 calf serum differed markedly one from the other, the heterogeneity being equally great among strains belonging to the same genomic group and those coming from different genomic groups. There appeared to be no relation between the genomic variability of *M. bovis* and the antigenic variability ...

Because Poumarat teaches that antigenic variability is as great within *Mycoplasma bovis* groups as across *Mycoplasma bovis* groups, Poumarat teaches that there would be no gain in antigenic variability from including more than one type of *Mycoplasma bovis* in a vaccine. That is, there would be no point in having more than one type of *Mycoplasma bovis* in a vaccine. Poumarat thus discourages one of ordinary skill in the art from including more than one biotype in a vaccine. This teaches away from the subject matter of claims 8-12, 31-39, and 46-51. Thus, these claims are non-obvious over Boothby, Thorns, and Poumarat.

With respect to claims 29-33 and 40-51 which require that the vaccine be protective against mastitis, the Applicants wish to point out that none of Boothby, Thorns, or Poumarat discloses such a vaccine. Nor does any combination of those references suggest how to obtain such a vaccine. Thus, these claims are non-obvious over Boothby, Thorns, and Poumarat.

The time for responding to the Office Action was set for December 30, 2003. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

Dated: MARCH 29, 2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,352	LEONARD ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 29-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-12 and 29-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed August 19, 2004. Claims 1, 3-8 and 10-12 have been amended. Claims 2 and 13-28 have been cancelled. Claims 29-56 have been added.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following Objection and Rejections have been withdrawn:

a) Objection to claim 22, page 3, paragraph 2 of previous Office action.

b) Objection to claim 21, page 3 paragraph 4 of previous Office action.

c) Rejection of claims 1-12, 21-22 and 24 under 35 U.S.C. 112, first paragraph, pages 3-5 paragraph 5 of previous Office action.

d) Rejection of claims 8-12, 21-22 and 24 under 35 U.S.C. 112, second paragraph, page 5 paragraph 6 of previous Office action.

e) Rejection of claims 1-12, 21-22, 24 and 27 under 35 U.S.C. 112, second paragraph, page 6 paragraph 7 of previous Office action.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Maintained

4. The rejection of claims 1, 3, 5-6 and newly submitted claims 29-30, 40-44 and 52-55 under 35 U.S.C. 102(b) is maintained for the reasons set forth on pages 6-7 paragraph 8 of the previous Office Action.

The rejection is on the grounds that the claims are drawn to a vaccine composition which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient and wherein the vaccine does not include saponin.

Boothby teaches a vaccine composition comprising killed *Mycoplasma bovis* and phosphate buffered saline (PBS) used for systemic immunization of calves (page 130). Boothby teaches that the vaccine preparations used contained 5.00 mg/ml of antigen for immunization (page 131) which meets the claim limitation " wherein the amount of each inactivated biotype is at least 10^8 *M. bovis* cells". Boothby teaches that cows vaccinated with *M. bovis* antigen in PBS elicited a moderate indirect hemagglutinations (IHA) response to systematic vaccination, an IgG ELISA response and an ELISA IgA response (page 133). Booth by et al teach that the highest respiratory IgA reactivity was found in the nasal secretions of the group which was vaccinated with *M. bovis* in PBS (page 134). Boothby et al teach that there was no sign of respiratory illness in any calves used in the study (page 136). Therefore, the vaccines were protective against respiratory infection caused by *M. bovis*.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the products of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges there are functional differences between the Boothby and the claimed invention. Applicant teaches that the vaccine of the claimed invention does not cause unfavorable or adverse reactions. Applicant urges that Boothby teaches vaccines that demonstrate unfavorable reactions. Applicant urges that newly submitted claims are not anticipated by Boothby. Applicant urges that newly added claim 29 recites that the vaccine is protective against *Mycoplasma bovis* mastitis. Applicant urges that the characteristic of being protective against mastitis is not simply an intended use but is a characteristic of the vaccine itself. Applicant urges that publications later than Boothby teach that

Boothby could not have disclosed a vaccine protective against mastitis. Applicant refers to Heller et al, 1993, Hanson, September 2001 and Hanson, October 2001. Applicant urges that newly submitted claims 34-39 recite "at least two inactivated or attenuated *Mycoplasma bovis* biotypes" and Boothby does not discloses more than a single biotype. Applicant urges that newly submitted claim 52 comprises an adjuvant that differs from the adjuvants listed in Boothby.

Applicant's arguments filed August 19, 2004 have been fully considered but they are not persuasive. The claims are directed to vaccine compositions comprising at least one inactivated *Mycoplasma bovis* biotype and pharmaceutically acceptable excipient. Boothby teach vaccine compositions comprising at least ~~on~~ one formalin inactivated *M. bovis* in PBS (pages 40 and 131) Boothby also teach that adjuvants such as Freund's incomplete adjuvant were used in the vaccine compositions (pages 131-132). Applicant is arguing limitations that are not in the claims with their assertion that "the vaccine compositions of the prior art cause adverse reactions and the claimed vaccine composition do not". There is no claim limitation regarding favorable, unfavorable or any kind of reactions as they relate to the claimed vaccine compositions. In response to applicant's argument regarding that "the claimed vaccines are protective against *Mycoplasma bovis* mastitis", the Examiner is viewing this limitation as limitation of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of

performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Applicant's referral to other publications (Heller et al, 1993, Hanson, September 2001 and Hanson, October 2001) to support their position is irrelevant since Boothby teach the claimed vaccine compositions. Applicant has not provided a side-by-side comparison to show that the vaccines of the prior art differ from the claimed vaccine. Therefore, it is the Examiner's position that Boothby anticipates the claimed invention. It should be noted that this rejection does not include claims 34-39 which recite "at least two inactivated or attenuated *M. bovis* biotypes.

5. The rejection of claims 1, 4, 5 and 7 and newly submitted claims 29-30 and 56 under 35 U.S.C. 102(b) is maintained for the reasons set forth on pages 8-9 paragraph 9 of the previous Office Action.

The rejection was on the grounds that Thorns et al teach attenuated bovine strains of *M. bovis*. Thorns et al teach that mice were inoculated with 0.1 of E medium (excipient) containing a known number of colony forming units (CFU) of *M. bovis*. Thorns et al teach that the attenuated strains (passaged more than 91-138 times) contained an inoculum per gland of 6.0-7.0 cells (cells measured (log_{10})(see Table 1, page 329). This amount meets the claim limitation "wherein the amount of each attenuated biotype is at least 10^5 *M. bovis* cells. Thorns et al teach that the *M. bovis* strains were passaged in liquid medium more than 60 times were markedly less virulent than the same or different strains with fewer passages. Thorns et al teach that the high passaged *M. bovis* strains were less virulent and produced only minor histopathological changes in vaccinated animals (see the Abstract). Thorns et al teach that mice inoculated with high passage *M. bovis* did not produce a systemic response (page 331). Thorns et al

teach that only one out of five in each of the group inoculated with *M. bovis* passaged 91 times showed signs inflammation (page 329, Table 1). Thorns et al teach that all mice that were inoculated with *M. bovis* passaged over 91 times had normal glands and showed not signs of systematic response (page 329, Table 1). Therefore, the mice vaccinated with *M. bovis* passaged over 91 times appeared to be protected against systematic response. Thorns et al teach that the modified strains of *M. bovis* (high passage strains) should provide further insight into the pathogenesis of *M. bovis* mastitis which could perhaps lead to a stable vaccine for this disease (page 332).

Since the Office does not have the facilities for examining and comparing applicant's vaccine with vaccine of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the products of the prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that there is no disclosure in Thorns et al that the attenuated strains were protective against any disease. Applicant urges that Thorns et al do not disclose any data that indicates that the attenuated strains cause any stimulation of the immune system in mice against *M. bovis*. Applicant points out the strains themselves were injected into mice. Applicant urges that there are no showing in Thorns et al that the disclosed attenuated *M. bovis* strains could be used as vaccines.

Applicant's arguments filed August 19, 2004 have been fully considered but they are not persuasive. The claims are directed to vaccine compositions comprising at least one attenuated *Mycoplasma bovis* biotype and pharmaceutically acceptable excipient. Thorns et al teach vaccine compositions comprising at least ~~one~~ one attenuated *M. bovis* biotype in 0.1 E medium (excipient). In response to applicant's argument regarding protection against any disease and stimulation of the immune system, these are claim limitations that are viewed

as imitations of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Applicant has not provided a side-by-side comparison to show that the vaccines of the prior art differ from the claimed vaccine. Therefore, it is the Examiner's position that Thorns et al anticipate the claimed invention.

6. The rejection of claims 1, 3-12 and newly submitted 29-56 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 9-12, paragraph 10 of the previous Office Action.

The rejection was on the grounds that Boothby teaches a vaccine composition comprising killed *Mycoplasma bovis* and phosphate buffered saline used for systemic immunization of calves (page 130). Boothby also teaches vaccine preparations comprising 0.5 ml killed *Mycoplasma bovis* antigen, 1 ml of Freund's incomplete adjuvant and 0.5ml of various aqueous solutions (page 131). Boothby teaches that the vaccine preparations used contained 5.00 mg/ml of antigen for immunization (page 131) which meets the claim limitations " wherein the amount of each inactivated biotype is at least 10^8 *M. bovis* cells". Boothby teaches that *M. bovis* is not highly immunogenic in the bovine. Boothby teaches that immunopotentiating effect of adjuvants may be used to prolonged deposition of antigen, modification the antigen or the recruitment and/or activation of the circulating lymphoid or reticuloendothelial cells (page 129). Boothby teach that adjuvants have been used in successful vaccine preparations of *M. bovis* and other pathogenic mycoplasmas. Boothby further teaches that adjuvants would be of particular benefit if found for local immunization where

lymphocytes and phagocytic cells are suppressed or where small amounts of antigen is preferred to avoid undesirable reactions (page 129).

Boothby does not teach the use of at least inactivated *M. bovis* biotypes.

Poumarat et al disclose 37 *Mycoplasma bovis* strains from 13 different genomic groups (i.e. biotypes)(see the Abstract). Poumarat et al disclose that based on the combination of the different electrophoretic profiles obtained with the three enzymes, the 37 strains could be classified in 13 genomic groups (table 2).

Boothby and Poumarat et al do not teach the use of attenuated *M. bovis* biotypes.

Thorns et al teach attenuated bovine strains of *M. bovis*. Thorns et al teach that mice were inoculated with 0.1 of E medium containing a known number of colony forming units (CFU) of *M. bovis*. Thorns et al teach that the attenuated strains (passaged more than 60 times) contained an inoculum per gland of 5.1-7.0 cells (cells measured (log_{10})((see Table 1, page 329). This amount meets the claim limitation "wherein the amount of each attenuated biotype is at least 10^5 *M. bovis* cells. Thorns et al teach that the *M. bovis* strains were passaged in liquid medium more than 60 times were markedly less virulent than the same or different strains with fewer passages. Thorns et al teach that the high passaged *M. bovis* strains were less virulent and produced only minor histopathological changes in vaccinated animals (see the Abstract). Thorns et al teach that the modified strains of *M. bovis* (high passage strains) should provide further insight into the pathogenesis of *M. bovis* mastitis which could perhaps lead to a stable vaccine for this disease (page 332).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the attenuated *M. bovis* strains of a taught by Thorns et al and the multiple *M. bovis* biotype isolates as taught by Poumarat et al and modify the vaccine composition comprising inactivated *M. bovis* and PBS to include a suitable adjuvant because Poumarat et al teach that there is a marked intraspecies genomic heterogeneity among isolates of *Mycoplasma bovis* collected from different geographic origins and that antigenic variability must be taken into account in developing diagnostic and vaccination strategies (page 319) and Thorns et al has demonstrated that high passaged *M. bovis* strains were less virulent and produced only minor histopathological changes in vaccinated animals and do not cause systematic changes in inoculated animals. Additionally, Boothby teaches that immunopotentiating effect of adjuvants may be used to prolonged deposition of antigen, modification the antigen or the recruitment and/or activation of the circulating lymphoid or reticuloendothelial cells (page 129). It would be expected that a vaccine composition comprising inactivated *M. bovis* strains of multiple biotypes, attenuated *M. bovis* strains of multiple biotypes, PBS and a suitable adjuvant would be effect against infections caused by *M. bovis.*

Applicant urges that Boothby does not disclose a vaccine that does not cause unfavorable reactions or a vaccine that is protective against mastitis. Applicant urges neither Thorns et al or Poumarat et al provide the subject matter that is missing in Boothby. Applicant urges that Thorns et al do not teach vaccines and certainly do not teach vaccines that do not cause unfavorable reactions or vaccines that are protective against mastitis. Applicant urges that Poumarat et al do not disclose any vaccines since Poumarat et al is limited to a study of the antigenic characteristics of certain strains of *Mycoplasma bovis*. Applicant urges that one of skill in the art would not could not arrive at the present invention by combining Thorns et al, Poumarat et al and Boothby.

Applicant's arguments filed August 19, 2004 have been fully considered but they are not persuasive. In response to applicant's argument that one of skill in the art would not have any suggestion to combine the references to arrive at the claimed invention, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). One of skill in the art would have been motivated to combine the teachings of the prior art because Poumarat et al teach that there is a marked intraspecies genomic heterogeneity among isolates of *Mycoplasma bovis* collected from different geographic origins and that antigenic variability must be

taken into account in developing diagnostic and vaccination strategies (page 319) and Thorns et al has demonstrated that high passaged *M. bovis* strains were less virulent and produced only minor histopathological changes in vaccinated animals and do not cause systematic changes in inoculated animals. Therefore, one of ordinary skill in the art would reasonably conclude that a vaccine composition comprising inactivated *M. bovis* strains of multiple biotypes, attenuated *M. bovis* strains of multiple biotypes, PBS and a suitable adjuvant would be effect against infections caused by *M. bovis*.

To address Applicant's comments regarding that the prior art references do not teach vaccine compositions that do not cause unfavorable reaction, it is the Examiner's position that Applicant is arguing limitations that are not in the claims. There is no claim limitation regarding favorable, unfavorable or any kind of reactions as they relate to the claimed vaccine compositions. To address Applicant's comments that the prior art references do not teach "vaccine compositions that are protective against mastitis", it is the Examiner's position that the claim limitation " the vaccine compositions are protective against *Mycoplasma bovis* clinical disease" is being viewed as a limitation of intended use. It should be remembered that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*,

370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). To address the claim limitations of the newly submitted claims, such as "biotypes are genetically different as determined by an analysis of DNA or RNA from biotypes", "wherein the analysis is PCR fingerprinting, analysis of ribosomal RNA or analysis of DNA polymophisms" "wherein the PCR fingerprinting uses as primer's SEQ ID NO:1 and SEQ ID NO:2" and "wherein the *M. bovis* biotype is inactivated and had been inactivated by treatment with formalin, azide, freeze-thawing, sonification, heat, sudden pressure drop, detergent, lysozyme, phenol, proteolytic enzymes, β-propiolactone, Thimerosal or binary ethyleneimine" would be viewed as process limitations. It should be remembered that the products of the prior art reference appear to be the same product claimed by the applicant because they appear to possess the same functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 29222-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects

inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon. There is nothing on the record to show that the combination of reference does not suggest the claimed invention.

Status of Claims

7. No claims allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
May 12, 2005

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER

INFORMATION DISCLOSURE STATEMENT BY APPLICANTS PTO FORM 1449	ATTY. DOCKET NO. 12780/101	SERIAL NO. 09/708,352
	APPLICANT(s) Joan D. LEONARD et al.	
	FILING DATE November 8, 2000	GROUP 1645

U. S. PATENT DOCUMENTS

EXAMINER INITIAL	PATENT NUMBER	PATENT DATE	NAME	CLASS	SUBCLASS	FILING DATE
	6,548,069	04/15/03	Hymas et al.			

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION	
						YES	NO

OTHER DOCUMENTS

EXAMINER INITIAL		AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.
		Razin et al., DNA Cleavage Patterns as Indicators of Genotypic Heterogeneity among Strains of Acholeplasma and Mycoplasma Species, Journal of General Microbiology 129:1935-1944 (1983)

EXAMINER	DATE CONSIDERED 5/11/05

EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 09/708,352	Applicant(s)/Patent Under Reexamination LEONARD ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Boothby (Immunologic Responses to Mycoplasma bovis, University Microfilm International (Dissertation) 1-172, 1982).
*	V	Poumarat et al (Veterinary Microbiology, 40, 1994, 305-321).
*	W	Thorns et al (Res. Vet. Sci., 1980, 29(3), 328-332).
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.